

IN THE SPECIFICATION

Please amend the specification as follows:

The paragraph beginning at the unnumbered page preceding page 1, line 2 is amended as follows:

The present invention relates to peptide inhibitors for preventing degradation of hypoxia-inducible factor 1 (HIF-1) and activating transcription of erythropoietin (EPO), vascular endothelial growth factor (VEGF), EPO, VEGF and various glycolytic enzymes. The invention further relates to methods of using those peptide inhibitors for a variety of therapeutic purposes, including treatment of tissues injured by trauma, heart attack, stroke or by diminished blood flow.

The paragraph beginning at page 1, line 12 is amended as follows:

Induction of HIF-1 activity by 1% O₂, CoCl₂, or desferrioxamine (DFX) ~~DFX~~ has been detected in many mammalian cell lines (Wang & Semenza (1993a) Proc. Natl. Acad. Sci. USA 90:4304-4308). Reporter genes linked to the EPO enhancer and transfected into non-EPO-producing cells were actively transcribed by hypoxia-inducible factor (Wang & Semenza (1993a) supra; Maxwell et al. (1993) Proc. Natl. Acad. Sci. USA 90:2423-2427). RNAs encoding several glycolytic enzymes were induced by 1% O₂, CoCl₂, or DFX in EPO-producing Hep3B or non-producing HeLa cells. However, cycloheximide blocked such induction. Moreover, glycolytic gene sequences containing HIF-1 binding sites exhibited hypoxia-inducible transcription in transfection assays (Firth et al. (1994) supra; Semenza et al. (1994) supra). These experiments support the role of HIF-1 in activating homeostatic responses to hypoxia.

The paragraph beginning at page 3, line 16 is amended as follows:

Acidic amino acids include, for example, aspartic acid or glutamic acid. Aliphatic amino acids include, for example, alanine, valine, leucine, isoleucine, ~~t-butylalanine~~, n-butylalanine, t-butylalanine, N-methylisoleucine, norleucine, N-methylvaline, cyclohexylalanine, β -alanine, N-methylglycine, or α -aminoisobutyric acid. Polar amino acids include, for ~~example~~ example, asparagine, glutamine, serine, threonine, tyrosine, citrulline, N-acetyl lysine, methionine sulfoxide, or homoserine. Apolar amino acids include, for example, methionine, glycine or

proline. Aromatic amino acids include, for example, phenylalanine, tyrosine, tryptophan, phenylglycine, naphthylalanine, β -2-thienylalanine, 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, pyridylalanine, or 3-benzothienyl alanine.

The paragraph beginning at page 8, line 17 is amended as follows:

There is no particular upper limit on peptide size. However, it is generally cheaper to make shorter peptides than longer peptides. Moreover, small peptides may diffuse and travel through membranes better. Hence, the peptide inhibitors of the invention are generally shorter than about one hundred amino acids. Desirable peptide inhibitors are shorter than about seventy five amino acids. More desirable peptide inhibitors are shorter than about fifty amino acids. Even more desirable peptides are shorter than about forty-five amino acids. Especially desirable peptides are shorter than about forty amino acids. Examples of desirable peptides include those with sequences related to SEQ ID NO:4 with eight amino acids, and SEQ ID NO:5 with nineteen amino acids.

MLA(Hyp)TIPM (SEQ ID NO:4)

DLDLEMLA(Hyp)YIPMDDDFQL (SEQ ID NO:5)

In the above sequences, (Hyp) indicates hydroxyproline.

The paragraph beginning at page 23, line 25 is amended as follows:

These ingredients can be included in beneficial amounts, for example, up to about 15 wt %, of zinc oxide may be added; typically 6-10% of zinc oxide is used, possibly in combination with another ingredient such as ichthammol (0-3 wt %) and/or calamine (0-15% wt %). Ichthammol or calamine may also be used alone. Chlorhexidine acetate can be used at a concentration of up to 1% by weight; 0.5 wt % is typical.

The paragraph beginning at page 25, line 30 is amended as follows:

Peptide Synthesis. In order to test our hypothesis that angiogenesis could be stimulated by selective inhibition of the action of the VBC complex on HIF-1 α , the following peptide

having SEQ ID NO:7 (termed the "ODD peptide") was synthesized using standard FMOC chemistry and purified by reverse phase HPLC:

YGRKKRRQRRR- DLDLEMLA(Hyp)YIPMDDDFQL (SEQ ID NO:7)